

ORGANIC COMPOUNDS

The present invention relates to trisubstituted furans, namely 2,2-disubstituted 5-methyl-2,5-dihydro- and 2,2-disubstituted 5-methyl-tetrahydrofurans and their use as odorants.

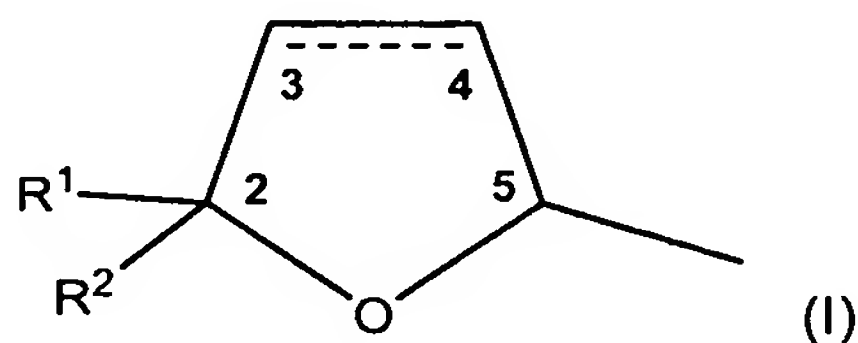
- 5 This invention relates furthermore to a method of their production and to fragrance compositions comprising them.

In the fragrance industry there is a constant demand for new compounds that enhance or improve on odour notes, or impart new odour notes.

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- It has now been found that certain trisubstituted furans constitute new powerful blackcurrant odorants devoid of any sulphur off-notes. Fruity, blackcurrant notes were first used in »Amazon» (Hermes, 1974), and became more and more trendy as top notes in perfumery as they can impart naturalness and freshness, and thus constitute attractive alternatives to hesperidic-citrus, lavender or aldehydic notes. Perfume examples for this recent trend include »Le Monde est beau» (Kenzo, 1997) and »In Love Again» (Yves Saint Laurent, 1998). Since then, blackcurrant notes became very popular and are today widely used, not only in fine fragrances, but also in the cosmetics and toiletries segment. However, most blackcurrant odorants, such as Corps Cassis (4-methyl-4-methylsulfanylpentan-2-one) and Oxane (2-methyl-4-propyl[1,3]oxathiane) are sulphury compounds and intense, sulfury-smelling by-products which may lead to unpleasant off-notes. Thus, there is a specific need for new blackcurrant odorants devoid of sulphur.

- 25 Accordingly, the present invention refers in one of its aspects to a compound of formula (I)



- 30 wherein

R¹ is methyl, ethyl, propyl or iso-propyl;

R² is a branched C₄ - C₇ alkyl, e.g. *tert*-butyl, *neo*-pentyl, or *iso*-hexyl; C₅ - C₈ cycloalkyl, e.g. cyclohexane and cycloheptane; or mono- or disubstituted C₅ or C₆ cycloalkyl, such as methylcyclohexyl and dimethylcyclohexyl; and

the bond between C-3 and C-4 is a single bond, or the dotted line together with the
 5 bond between C-3 and C-4 represents a double bond.

The compounds according to the present invention contain several chiral centres, and as such may exist as a mixture of stereoisomers, or they may be resolved as isomerically pure forms. Resolving stereoisomers adds to the complexity of
 10 manufacture and purification of these compounds, and so it is preferred to use the compounds as mixtures of their stereoisomers simply for economic reasons. However, if it is desired to prepare individual stereoisomers, this may be achieved according to methodology known in the art, e.g. preparative HPLC and GC or by stereoselective synthesis.

15 Particular preferred compounds of formula (I) are 2-*tert*-butyl-5-methyl-2-propyl-2,5-dihydrofuran, 2-*tert*-butyl-5-methyl-2-propyltetrahydrofuran, 2-*tert*-butyl-2-isopropyl-5-methyl-2,5-dihydrofuran, 2-*tert*-butyl-2-isopropyl-5-methyltetrahydrofuran, 2-*tert*-butyl-2-ethyl-5-methyl-2,5-dihydrofuran, 2-*tert*-butyl-2-ethyl-5-methyltetrahydrofuran, 2-*tert*-
 20 butyl-2,5-dimethyl-2,5-dihydrofuran, 2-*tert*-butyl-2,5-dimethyltetrahydrofuran, 2-(3',3'-dimethylcyclohexyl)-2,5-dimethyl-2,5-dihydrofuran, and 2-(3',3'-dimethylcyclohexyl)-2,5-dimethyltetrahydrofuran.

The compounds according to the present invention may be used alone or in
 25 combination with a base material. As used herein, the "base material" includes all known odorant molecules selected from the extensive range of natural products and synthetic molecules currently available, such as essential oils, alcohols, aldehydes and ketones, ethers and acetals, esters and lactones, hetero- and macrocycles, as well as nitrogen-containing compounds, and/or in admixture with one or more ingredients or
 30 excipients conventionally used in conjunction with odorants in fragrance compositions, for example, carrier materials, and other auxiliary agents commonly used in the art.

The following list comprises examples of known odoriferous molecules, which may be combined with the compounds of the present invention:

essential oils and extracts, e.g. angelica root oil, bergamot oil, blackcurrant absolute, buchu leaf oil, coriander oil, geranium oil, grapefruit oil, jasmine absolute, lavender oil, lime oil, neroli oil, oakmoss absolute, orris root oil, patchouli oil, petitgrain oil, rose oil, or ylang-ylang oil.

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alcohols, e.g. citronellol, dimethyl benzyl carbinol, eugenol, geraniol, (3Z)-hex-3-enol, linalool, phenylethyl alcohol, Super Muguet[®], terpineol, or Undecavertol[®].

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aldehydes and ketones, e.g. Cetone V[™], damascenone, heliotropine, α -hexylcinnam aldehyde, Iso E Super[®], β -ionone, Isoraldeine[®], Silvial[®], or vanillin.

ethers and acetals, e.g. Ambrox[™], Oxane[™] or Spirambrene[™].

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esters and lactones, e.g. benzyl acetate, coumarin, Hedione[®], or hexyl salicylate.

hetero- and macrocycles, e.g. ambrettolide, ethylene brassylate, Exaltolide[®], maltol, Moxalone[™], or Nirvanolide[®].

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nitrogen-containing compounds, e.g. methyl anthranilate, Peonile[®], or Stemone[®].

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The compounds of the present invention may be used in a broad range of fragrance applications, e.g. in any field of fine and functional perfumery, such as perfumes, household products, laundry products, body care products and cosmetics. The compounds can be employed in widely varying amounts, depending upon the specific application and on the nature and quantity of other odourant ingredients. The proportion is typically from 0.001 to 5 weight percent of the application. In one embodiment, compounds of the present invention may be employed in a fabric softener in an amount of from 0.001 to 0.05 weight percent. In another embodiment, compounds of the present invention may be used in fine perfumery in amounts of from 0.1 to 5 weight percent, more preferably between 0.1 and 2 weight percent. However, these values are given only by way of example, since the experienced perfumer may also achieve effects or may create novel accords with lower or higher concentrations.

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The compounds of the present invention may be employed into the fragrance application simply by directly mixing the fragrance composition with the fragrance application, or they may, in an earlier step, be entrapped with an entrapment material, examples of which include polymers, capsules, microcapsules and nanocapsules, liposomes, film formers, absorbents such as carbon or zeolites, cyclic oligosaccharides and mixtures thereof, or they may be chemically bonded to substrates, which are adapted to release the fragrance molecule upon application of an external stimulus such as light, enzyme, or the like, and then mixed with the application.

Thus, the invention additionally provides a method of manufacturing a fragrance application, comprising the incorporation of a compound of formula (I) as a fragrance ingredient, either by directly admixing the compound to the application or by admixing a fragrance composition comprising a compound of formula (I), which may then be mixed to a fragrance application, using conventional techniques and methods.

As used herein, "fragrance application" means any products, such as fine fragrances, e.g. eau de perfumes and eau de toilettes; household products, e.g. detergents for dishwasher, surface cleaner; laundry products, e.g. softener, bleach, detergent; body care products, e.g. shampoo, shower gel; and cosmetics, e.g. deodorants, vanishing cremes, comprising an odorant. This list of products is given by way of illustration and is not to be regarded as being in any way limiting.

Compounds of formula (I) may be prepared by the reaction of magnesium Grignard reagent of 3-butyne-2-ol, prepared according to a general procedure well known in the art, with a corresponding ketone (R^1R^2CO) resulting in an alkynediol. The alkynediol is then hydrogenated in the presence of a Lindlar catalyst. Subsequent cyclisation of the formed *cis*-configured alkenediol in the presence of potassium hydrogensulfate results in the formation of the corresponding 5-methyl-2,5-dihydrofuran. Further compounds of formula (I) may be prepared by hydrogenation of the dihydrofuranes.

The invention is now further described with reference to the following non-limiting examples.

Example 1: 2-*tert*-Butyl-5-methyl-2-propyl-2,5-dihydrofuran

Over a period of 30 min, a solution of 40.7 g (374 mmol) of ethyl bromide in 100 mL of dry tetrahydrofuran was added dropwise to a stirred suspension of 9.08 g (374 mmol) of

magnesium turnings in 5 mL of dry tetrahydrofuran, with the reaction being initiated by occasional heating with a heat gun. The reaction mixture was then stirred for additional 3 h at reflux. The reaction was allowed to cool down to room temp., and a solution of 12.6 g (180 mmol) of but-3-yn-2-ol in 80 mL of dry tetrahydrofuran was added dropwise with stirring. The reaction mixture was then again heated to reflux for 4 h, prior to removal of the heating bath. At room temp., a solution of 25.0 g (195 mmol) of 2,2-dimethylhexan-3-one in 90 mL of dry tetrahydrofuran was added with stirring within 35 min, and the reaction mixture was refluxed for another 2 d with stirring. The reaction mixture was then allowed to cool to room temp., and quenched with 500 mL of an aqueous satd. NH_4Cl solution. The aqueous layer was extracted three times with 500 mL of ether each, the combined organic extracts were dried with sodium sulfate, and the solvent was evaporated on a rotary evaporator to provide 32.3 g (90%) of crude 5-*tert*-butyloct-3-yne-2,5-diol as a slightly yellowish oil, which was employed without further purification. A solution of 20.8 g (105 mmol) of this product in 300 mL of ethanol was hydrogenated by stirring at ambient pressure and temp. in an atmosphere of hydrogen in the presence of 3.11 g (2.92 mmol) of 10% palladium on barium sulfate and 300 mg (2.32 mmol) of quinoline. After 10 h of stirring, the catalyst was filtered off over a pad of Celite, and the solvent was removed on a rotary evaporator to provide 20.7 g (99%) of crude (3*Z*)-5-*tert*-butyloct-3-ene-2,5-diol, of which 19.6 g (98 mmol) was heated for 45 min in a Kugelrohr apparatus to 155°C / 280 mbar in the presence of 2.00 g (14.7 mmol) of KHSO_4 . The evaporating reaction product was trapped in a bulb at -80°C, and further purified by flash chromatography (400 g of silica-gel, pentane/ether, 98:2) to afford 7.26 g of product. This was then distilled in a Kugelrohr apparatus to furnish at 70–80°C / 20 mbar 6.24 g (34%) of the title compound as a colorless odoriferous liquid.

IR (film): $\nu = 1110 / 1047$ (ν C–O–C), 1365 / 1353 (δ_s CH_3), 977 (δ C=C–H), 1466 / 1480 (δ_{as} CH_3), 1715 (ν C=C, ring), 3074 (ν C=C–H) cm^{-1} . – ^1H NMR (CDCl_3): $\delta = 0.88 / 0.91$ (t, $J = 7.0$ Hz, 3H, 3''- H_3), 0.90 (s, 9H, 1'- Me_3), 1.23 / 1.25 (2d, $J = 6.5$ Hz, 3H, 5-Me), 1.42–1.50 (m, 2H, 2''- H_2), 1.68–1.74 (m, 2H, 1''- H_2), 4.87–4.88 (m, 1H, 5-H), 5.55 / 5.57 (2dd, $J = 6.0, 2.5$ Hz, 1H, 4-H), 5.70 / 5.72 (2d, $J = 6.0$ Hz, 1H, 3-H). – ^{13}C NMR (CDCl_3): $\delta = 14.9 / 15.0$ (2q, C-3''), 17.2 / 17.4 (2t, C-2''), 18.4 / 18.7 (2q, 5-Me), 21.4 / 21.8 (2t, C-1''), 26.1 / 26.7 (2q, 1'- Me_3), 35.5 / 37.2 (2s, C-1'), 82.8 / 82.9 (2d, C-5), 98.4 / 98.6 (2s, C-2), 130.2 / 130.5 / 131.2 / 131.7 (4d, C-3,-4). – MS (EI): m/e (%) = 57 (17)

[C₄H₉⁺], 83 (9) [C₅H₇O⁺], 125 (100) [M⁺ – C₄H₉], 139 (8) [M⁺ – C₃H₇], 167 (5) [M⁺ – CH₃].

Odor description: Blackcurrant, natural, rich, eucalyptus buds, anis, buchu leaves,
5 slightly green.

Example 2: 2-*tert*-Butyl-5-methyl-2-propyltetrahydrofuran

At ambient temp., a suspension of 2.91 g (10.4 mmol) of 2-*tert*-butyl-5-methyl-2-propyl-
10 2,5-dihydrofuran and 1.06 g (1.00 mmol) of 10% palladium on activated charcoal in 60 mL of dry ether was hydrogenated for 4 h in a Parr apparatus at 2.5 bar hydrogen pressure. The catalyst was filtered off over a pad of Celite, and the solvent evaporated. The resulting residue was distilled in a Kugelrohr apparatus to provide at 75–85°C / 20 mbar 2.43 g (80%) of the title compound as a colorless odoriferous liquid.

15 IR (film): ν = 1110 / 1088 (ν C–O–C), 1379 / 1365 (δ_s CH₃), 1466 / 1480 (δ_{as} CH₃), 985 (ν_r CH₂) cm^{–1}. – ¹H NMR (CDCl₃): δ = 0.88 / 0.91 (t, J = 7.0 Hz, 3H, 3''-H₃), 0.90 (s, 9H, 1'-Me₃), 1.19 / 1.21 (2d, J = 6.0 Hz, 3H, 5-Me), 1.33–1.40 (m, 2H, 2''-H₂), 1.41–1.45 (m, 2H, 1''-H₂), 1.69–1.76 (m, 2H, 3-H₂), 1.79–1.88 (m, 2H, 4-H₂), 4.05 (br. quint., J = 6.0
20 Hz, 1H, 5-H). – ¹³C NMR (CDCl₃): δ = 15.2 / 15.3 (2q, C-3''), 18.0 / 18.2 (2t, C-2''), 21.2 / 21.3 (2q, 5-Me), 26.3 / 26.3 (2q, 1'-Me₃), 31.2 / 31.5 (2t, C-4), 35.7 / 36.0 (2t, C-3), 38.2 / 38.7 (2t, C-1''), 39.5 / 39.6 (2s, C-1'), 76.6 / 77.0 (2d, C-5), 89.0 / 90.2 (2s, C-2). – MS (EI): m/e (%) = 57 (30) [C₄H₉⁺], 71 (100) [M⁺ – C₈H₁₇], 85 (6) [C₄H₉O⁺], 127 (76) [M⁺ – C₄H₉], 141 (5) [M⁺ – C₃H₇], 169 (5) [M⁺ – CH₃].

25 Odor description: Blackcurrant, damascone, sweet, natural, rich, with green, piny, eucalyptus and mint-like facets.

30 Example 3: 2-*tert*-Butyl-2-isopropyl-5-methyl-2,5-dihydrofuran

Following the general procedure of example 1, 5-isopropyl-6,6-dimethylhept-3-yne-2,5-diol was prepared in 78% yield by reaction of 2,2,4-trimethylpentan-3-one with the previously prepared Grignard reagent of but-3-yn-2-ol. Lindlar hydrogenation of a solution of 18.1 g (90.0 mmol) of this material in 300 mL of dry ethanol in the presence

of 2.20 g (2.07 mmol) of 10% palladium on barium sulfate and 320 mg (2.48 mmol) of quinoline according to example 1 provided after analogous work-up 17.9 g (99%) of (3Z)-5-isopropyl-6,6-dimethylhept-3-ene-2,5-diol, of which 17.2 g (85 mmol) was heated in a Kugelrohr apparatus to 155°C / 280 mbar in the presence of 1.71 g (12.5 mmol) of KHSO₄ to furnish after trapping of the evaporating product at –80°C and flash chromatography (400 g of silica gel, pentane/ether, 98:2) 8.32 g of a colorless oil. This product was further purified by Kugelrohr distillation to afford at 80–90°C / 20 mbar 7.52 g (48%) of the title compound as a colorless odoriferous liquid.

- 10 IR (film): ν = 1111 / 1079 (ν C–O–C), 1366 / 1353 (δ_s CH₃), 983 (δ C=C–H), 1468 / 1481 (δ_{as} CH₃), 1712 (ν C=C, ring), 3071 (ν C=C–H) cm^{–1}. – ¹H NMR (CDCl₃): δ = 0.88 / 0.89 / 0.91 / 0.92 (4d, J = 6.0 Hz, 6H, 1''-Me₂), 0.95 (s, 9H, 1'-Me₃), 1.23 / 1.26 (2d, J = 6.5 Hz, 3H, 5-Me), 2.12 / 2.26 (m, 1H, 1''-H), 4.80–4.86 (m, 1H, 5-H), 5.67 / 5.68 (2dd, J = 6.0, 2.5 Hz, 1H, 4-H), 5.73 / 5.75 (2d, J = 6.0 Hz, 1H, 3-H). – ¹³C NMR (CDCl₃): δ = 19.6 / 19.7 (2q, 5-Me), 20.6 / 20.8 / 21.3 / 21.7 (4q, 1''-Me₂), 26.5 / 27.2 (2q, 1'-Me₃), 31.4 / 34.1 (2d, C-1''), 37.6 / 40.6 (2s, C-1'), 82.1 / 82.2 (2d, C-5), 99.6 / 99.7 (2s, C-2), 128.5 / 128.6 / 130.4 / 131.1 (4d, C-3,-4). – MS (EI): m/e (%) = 57 (100) [C₄H₉⁺], 83 (45) [C₅H₇O⁺], 125 (67) [M⁺ – C₄H₉], 139 (56) [M⁺ – C₃H₇], 167 (5) [M⁺ – CH₃].
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- 20 Odor description: Blackcurrant, fruity, grape, fresh with slightly metallic green nuances.

Example 4: 2-*tert*-Butyl-2-isopropyl-5-methyltetrahydrofuran

Following the general procedure of example 2, 2-*tert*-butyl-2-isopropyl-5-methyltetrahydrofuran was prepared from 3.61 g (19.8 mmol) of 2-*tert*-butyl-2-isopropyl-5-methyl-2,5-dihydrofuran by hydrogenation in the presence of 1.21 g (1.14 mmol) of 10% palladium on activated charcoal. Purification of the crude product by Kugelrohr distillation at 85–95°C / 20 mbar furnished 3.42 g (93%) of the title compound as a colorless odoriferous liquid.

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IR (film): ν = 1085 (ν C–O–C), 993 (ν_r CH₂), 1382 / 1366 (δ_s CH₃), 1478 (δ_{as} CH₃) cm^{–1}. – ¹H NMR (CDCl₃): δ = 0.89 / 0.92 (2d, J = 6.5 Hz, 6H, 1''-Me₂), 0.94 (s, 9H, 1'-Me₃), 1.19 / 1.23 (2d, J = 6.0 Hz, 3H, 5-Me), 1.75–1.79 (m, 2H, 4-H₂), 1.80–1.88 (m, 2H, 3-H₂), 2.06 / 2.25 (2 sept., J = 7.0 Hz, 1H, 1''-H), 3.97–4.05 (m, 1H, 5-H). – ¹³C NMR (CDCl₃):

δ = 19.7 / 20.6 (2q, 5-Me), 20.6 / 20.7 / 20.8 / 20.9 (4q, 1''-Me₂), 26.8 / 27.0 (2q, 1'-Me₃), 27.1 / 27.2 (2t, C-4), 29.2 / 33.3 (2d, C-1''), 34.4 / 35.9 (2t, C-3), 39.1 / 40.1 (2s, C-1'), 75.8 / 76.0 (2d, C-5), 91.8 / 92.4 (2s, C-2). – MS (EI): m/e (%) = 57 (95) [C₄H₉⁺], 71 (100) [M⁺ – C₈H₁₇], 85 (17) [C₅H₉O⁺], 127 (61) [M⁺ – C₄H₉], 141 (77) [M⁺ – C₃H₇], 169 (5) [M⁺ – CH₃].

Odor description: Blackcurrant, fruity, green, sweet, coumarin-like with floral and camphoraceous undertones.

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Example 5: 2-*tert*-Butyl-2-ethyl-5-methyl-2,5-dihydrofuran

Following the general procedure of example 1, 5-ethyl-6,6-dimethylhept-3-yne-2,5-diol was prepared in 83% yield by reaction of 2,2-dimethylpentan-3-one with the previously prepared Grignard reagent of but-3-yn-2-ol. Lindlar hydrogenation of a solution of 32.1 g (161 mmol) of this material in 400 mL of dry ethanol in the presence of 2.81 g (2.64 mmol) of 10% palladium on barium sulfate and 1.05 g (8.12 mmol) of quinoline provided after standard work-up 31.4 g (97%) of (3Z)-5-ethyl-6,6-dimethylhept-3-ene-2,5-diol, of which 21.2 g (112 mmol) was cyclised at 155°C / 280 mbar in the presence of 2.55 g (18.7 mmol) of KHSO₄ to afford after purification by flash chromatography (600 g of silica gel, pentane/ether, 98:2) 10.1 g of the corresponding dihydrofuran. Distillation at 70–80°C / 20 mbar provided 6.62 g (36%) of the title compound as a colorless odoriferous liquid.

IR (film): ν = 1102 / 1084 (ν C–O–C), 967 (δ C=C–H), 1365 / 1352 (δ_s CH₃), 1465 / 1479 (δ_{as} CH₃), 1705 (ν C=C, ring), 3073 (ν C=C–H) cm^{–1}. – ¹H NMR (CDCl₃): δ = 0.77 / 0.81 (2t, J = 7.5 Hz, 3H, 2''-H₃), 0.91 / 0.93 (2s, 9H, 1'-Me₃), 1.24 / 1.26 (2d, J = 6.5 Hz, 3H, 5-Me), 1.53–1.65 (m, 2H, 1''-H₂), 4.82–4.93 (m, 1H, 5-H), 5.54 / 5.56 (2dd, J = 6.0, 2.5 Hz, 1H, 4-H), 5.74 / 5.76 (2d, J = 6.0 Hz, 1H, 3-H). – ¹³C NMR (CDCl₃): δ = 8.1 / 9.3 (2q, C-2''), 21.1 / 21.4 (2q, 5-Me), 24.9 / 26.8 (2t, C-1''), 25.8 / 27.4 (2q, 1'-Me₃), 36.6 / 39.4 (2s, C-1'), 82.5 / 82.8 (2d, C-5), 98.4 / 98.7 (2s, C-2), 129.3 / 129.8 / 131.2 / 131.8 (4d, C-3,-4). – MS (EI): m/e (%) = 57 (26) [C₄H₉⁺], 83 (6) [C₅H₇O⁺], 111 (100) [M⁺ – C₄H₉], 139 (9), [M⁺ – C₂H₅], 153 (3) [M⁺ – CH₃].

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Odor description: Camphoraceous, fruity, blackcurrant, fresh, with green-metallic and animalic nuances.

5 Example 6: 2-*tert*-Butyl-2-ethyl-5-methyltetrahydrofuran

Analogous to the procedure of example 2, by hydrogenation of 3.12 g (18.4 mmol) of 2-*tert*-butyl-2-isopropyl-5-methyl-2,5-dihydrofuran in the presence of 1.20 g (1.12 mmol) of 10% palladium on activated charcoal. Kugelrohr distillation of the reaction product provided at 70–80°C / 20 mbar 3.42 g (93%) of the title compound as a colorless
10 odoriferous liquid.

IR (film): ν = 1106 / 1083 (ν C–O–C), 977 (ν_r CH₂), 1364 / 1380 (δ_s CH₃), 1479 (δ_{as} CH₃) cm⁻¹. – ¹H NMR (CDCl₃): δ = 0.84–0.95 (m, 3H, 2''-H₃), 0.90 / 0.92 (2s, 9H, 1'-Me₃), 1.20 / 1.22 (2d, J = 8.0 Hz, 3H, 5-Me), 1.36–1.46 (m, 2H, 3-H₂), 1.58–1.76 (m, 2H, 1''-H₂), 1.79–1.93 (m, 2H, 4-H₂), 3.94–4.11 (m, 1H, 5-H). – ¹³C NMR (CDCl₃): δ = 8.9 / 9.0 (2q, C-2''), 20.9 / 21.0 (2q, 5-Me), 26.0 / 26.5 (2q, 1'-Me₃), 27.9 / 28.0 (2t, C-1''), 28.7 / 30.2 (2t, C-3), 35.3 / 35.8 (2t, C-4), 38.0 / 39.3 (2s, C-1'), 76.5 / 76.7 (2d, C-5), 89.8 / 90.1 (2s, C-2). – MS (EI): m/e (%) = 57 (100) [C₄H₉⁺], 85 (7) [C₅H₉O⁺], 113 (59) [M⁺ – C₄H₉], 141 (21) [M⁺ – C₂H₅], 153 (5) [M⁺ – CH₃].
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Odor description: Fruity, minty, camphoraceous, blackcurrant, with metallic and animalic undertones.

25 Example 7: 2-*tert*-Butyl-2,5-dimethyl-2,5-dihydrofuran

Following the general procedure of example 1, 5,6,6-trimethylhept-3-yne-2,5-diol was prepared in 96% yield by reaction of 3,3-dimethylbutan-2-one with the previously prepared Grignard reagent of but-3-yn-2-ol. Lindlar hydrogenation of 10.2 g (60.0 mmol) of a solution of this material in 200 mL of dry ethanol in the presence of 960 mg (0.90 mmol) of 10% palladium on barium sulfate and 360 mg (2.78 mmol) of quinoline
30 provided after the usual work-up 10.2 g (100%) (3*Z*)-5,6,6-trimethylhept-3-ene-2,5-diol, of which 9.80 g (57.0 mmol) was cyclized in a Kugelrohr apparatus at 155°C / 280 mbar in the presence of 1.14 g (8.37 mmol) of KHSO₄ to afford after flash chromatography (200 g of silica gel, pentane/ether, 98:2) 2.61 g of the corresponding dihydrofuran.

Distillation in vacuo at 45–50°C / 20 mbar provided 2.35 g (26%) of the title compound as colorless odoriferous liquid.

IR (film): ν = 1102 / 1095 (ν C–O–C), 1367 / 1350 (δ_s CH₃), 946 (δ C=C–H), 1454 / 1479 (δ_{as} CH₃), 1709 (ν C=C, ring), 3075 (ν C=C–H) cm^{–1}. – ¹H NMR (CDCl₃): δ = 0.91 / 0.92 (2s, 9H, 1'-Me₃), 1.21 / 1.22 (2s, 3H, 2-Me), 1.24 / 1.26 (2d, J = 6.5 Hz, 3H, 5-Me), 4.82–4.92 (m, 1H, 5-H), 5.56 / 5.62 (2dd, J = 6.0, 1.5 Hz, 1H, 4-H), 5.76 / 5.79 (2d, J = 6.0 Hz, 1H, 3-H). – ¹³C NMR (CDCl₃): δ = 20.9 / 21.1 (2q, 5-Me), 23.3 / 24.2 (2q, 2-Me), 25.7 / 26.1 (2q, 1'-Me₃), 36.2 / 38.3 (2s, C-1'), 80.1 / 82.4 (2d, C-5), 95.0 / 95.2 (2s, C-2), 129.8 / 130.4 / 132.1 / 132.7 (4d, C-3,-4). – MS (EI): m/e (%) = 57 (10) [C₄H₉⁺], 83 (5) [C₅H₇O⁺], 97 (100) [M⁺ – C₄H₉], 139 (5) [M⁺ – CH₃].

Odor description: Blackcurrant, citric, limette, green and slightly fatty.

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Example 8: 2-*tert*-Butyl-2,5-dimethyltetrahydrofuran

According to the procedure of example 2, by hydrogenation of 1.62 g (10.3 mmol) of 2-*tert*-butyl-2,5-dimethyl-2,5-dihydrofuran in the presence of 600 mg (0.56 mmol) of 10% palladium on activated charcoal. Kugelrohr distillation furnished at 45–50°C / 20 mbar 1.37 g (82%) of the title compound as a colorless odoriferous liquid.

IR (film): ν = 1102 (ν C–O–C), 1368 / 1380 (δ_s CH₃), 1473 / 1478 (δ_{as} CH₃), 953 (ν_r CH₂) cm^{–1}. – ¹H NMR (CDCl₃): δ = 0.92 (s, 9H, 1'-Me₃), 1.13 / 1.15 (2s, 3H, 2-Me), 1.19 / 1.21 (2d, J = 6.0 Hz, 3H, 5-Me), 1.32–1.57 (m, 2H, 3-H₂), 1.98–2.01 (m, 2H, 4-H₂), 3.88–4.12 (m, 1H, 5-H). – ¹³C NMR (CDCl₃): δ = 20.9 / 22.4 (2q, 5-Me), 22.1 / 24.3 (2q, 2-Me), 25.7 (q, 1'-Me₃), 26.5 / 27.3 (2t, C-3), 33.9 / 34.4 (2t, C-4), 36.8 / 37.8 (2s, C-1'), 73.6 (d, C-5), 87.6 (s, C-2). – MS (EI): m/e (%) = 57 (28) [C₄H₉⁺], 85 (5) [C₄H₉O⁺], 99 (100) [M⁺ – C₄H₉], 141 (8) [M⁺ – CH₃].

Odor description: Green, camphoraceous, blackcurrant-like with some slight reminiscence to orange blossoms.

Example 9: 2-(3',3'-Dimethylcyclohexyl)-2,5-dimethyl-2,5-dihydrofuran

Following the general procedure of example 1, 2-(3',3'-dimethylcyclohexyl)hex-3-yne-2,5-diol was prepared in 62% yield by reaction of 1-(3',3'-dimethylcyclohexyl)ethanone with the previously prepared Grignard reagent of but-3-yn-2-ol. Lindlar hydrogenation of 10.0 g (44.6 mmol) of a solution of this material in 250 mL of dry ethanol in the presence of 740 mg (0.695 mmol) of 10% palladium on barium sulfate and 290 mg (2.24 mmol) of quinoline provided after the usual work-up 9.82 g (97%) (3Z)-2-(3',3'-dimethylcyclohexyl)hex-3-ene-2,5-diol, which was cyclized in a Kugelrohr apparatus at 180°C / 20 mbar in the presence of 430 mg (3.16 mmol) of KHSO₄. The resulting product was purified by flash chromatography (200 g of silica gel, pentane/ether, 99:1) and subsequent Kugelrohr distillation to provide at 55–60°C / 0.1 mbar 1.46 g (16%) of the title compound as colorless odoriferous liquid.

IR (film): ν = 824 (δ C=C–H), 1085 / 1105 (ν C–O–C), 1366 / 1350 (δ_s CH₃), 970 (ν_r CH₂), 1453 (δ_{as} CH₃) cm^{–1}. – ¹H NMR (CDCl₃): δ = 0.84–1.74 (m, 9H, 1'-H, 2'-,4'-,5'-,6'-H₂), 0.87 / 0.88 / 0.90 / 0.91 (2s, 6H, 3'-Me₂), 1.20 / 1.21 (2s, 3H, 2-Me), 1.24 / 1.25 / 1.25 / 1.26 (4d, J = 6.5 Hz, 3H, 5-Me), 4.81–4.92 (m, 1H, 5-H), 5.62 / 5.64 / 5.64 / 5.65 (4dd, J = 6.0, 1.5 Hz, 1H, 4-H), 5.67 / 5.68 / 5.69 / 5.70 (4d, J = 6.0 Hz, 1H, 3-H). – ¹³C NMR (CDCl₃): δ = 14.0 / 21.5 / 21.6 / 22.3 (4q, 5-Me), 22.3 / 22.4 (2t, C-5'), 23.2 / 23.9 / 24.6 / 24.7 / 26.6 / 28.2 (6q, 2-Me, 3'-Me axial), 27.2 / 27.8 / 27.9 / 28.2 (4t, C-6'), 30.7 / 30.8 (2s, C-3'), 33.6 / 34.1 (2q, 3'-Me equat.), 39.1 / 39.2 (2t, C-2'), 40.7 / 41.4 (2t, C-4'), 42.3 / 42.5 / 43.4 / 43.5 (4d, C-1'), 79.9 / 80.0 / 81.7 / 81.8 (4d, C-5), 92.3 / 92.4 / 92.5 / 92.6 (4s, C-2), 129.9 / 130.0 / 130.4 / 130.5 / 132.1 / 132.2 / 132.6 / 133.0 (8d, C-3,-4). – MS (EI): m/e (%) = 43 (14) [C₃H₇⁺], 55 (6) [C₄H₇⁺], 69 (6) [C₅H₉⁺], 79 (4) [M⁺ – C₈H₁₅ – H₂O], 97 (100) [M⁺ – C₈H₁₅], 175 (1) [M⁺ – CH₃ – CH₃], 193 (1) [M⁺ – CH₃], 208 (1) [M⁺].

Odor description: Fruity, blackcurrant, grapefruit, natural, green tomato vine, with aspects of apple and rhubarb.

Example 10: 2-(3',3'-Dimethylcyclohexyl)-2,5-dimethyltetrahydrofuran

According to the procedure of example 2, by hydrogenation of 1.00 g (4.80 mmol) of 2-(3',3'-dimethylcyclohexyl)-2,5-dimethyl-2,5-dihydrofuran in the presence of 100 mg

(0.0940 mmol) of 10% palladium on activated charcoal. Kugelrohr distillation furnished at 65–70°C / 0.1 mbar 690 mg (68%) of the title compound as a colorless odoriferous liquid.

- 5 IR (film): ν = 1094 (ν C–O–C), 953 (ν_r CH₂), 1455 (δ_{as} CH₃), 1374 (δ_s CH₃) cm⁻¹. – ¹H NMR (CDCl₃): δ = 0.82–1.82 (m, 11H, 1'-H, 3-,2'-,4'-,5'-,6'-H₂), 0.89 / 0.91 (2s, 6H, 3'-Me₂), 1.10 / 1.11 (2s, 3H, 2-Me), 1.20 / 1.23 (2d, J = 6.0 Hz, 3H, 5-Me), 1.93–2.09 (m, 2H, 4-H₂), 3.94–4.09 (m, 1H, 5-H). – ¹³C NMR (CDCl₃): δ = 21.2 / 21.3 / 21.9 / 22.4 / 23.3 / 24.2 / 24.4 / 24.7 (q, 2-,5-Me, 3'-Me axial), 22.5 / 22.6 (2t, C-5'), 27.6 / 27.7 / 27.8 / 27.8 (4t, C-3), 30.7 / 30.8 (2s, C-3'), 33.7 / 33.8 (2q, 3'-Me equat.), 33.7 / 34.0 / 34.5 / 35.2 / 35.6 / 36.1 (6t, C-4,-6'), 39.4 / 40.8 / 41.0 / 41.2 (4t, C-2',-4'), 43.2 / 43.4 / 43.5 / 43.6 (4d, C-1'), 73.4 / 73.5 / 75.0 / 75.1 (4d, C-5), 85.0 / 85.1 (2s, C-2). – MS (EI): m/e (%) = 43 (38) [C₃H₇⁺], 55 (9) [C₄H₇⁺], 69 (6) [C₅H₉⁺], 81 (3) [M⁺ – C₈H₁₅ – H₂O], 99 (100) [M⁺ – C₈H₁₅], 111 (3) [C₈H₁₅⁺], 138 (1) [C₁₀H₁₈⁺], 177 (1) [M⁺ – CH₃ – H₂O], 195 (2) [M⁺ – CH₃].
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Odor description: Sweet, floral-fruity, with green and blackcurrant-like facets.

20 Example 11: Fruity-Floral Accord for Female Perfumes

	Ingredient	Parts per weight
	1. Benzyl acetate	40
25	2. 2-Cyclohexyl-2-phenylacetone nitrile	80
	3. Damascenone at 1% in dipropylene glycol	30
	4. γ -Decalactone	4
	5. 3,7-Dimethyloct-6-en-1-ol	10
	6. 1,1-Dimethyl-2-phenylethyl acetate	20
30	7. 1,1-Dimethyl-2-phenylethyl butanoate	20
	8. Ethyl butanoate	10
	9. Ethyl maltol at 10% in dipropylene glycol	4
	10. Ethyl 2-methylbutanoate	2
	11. Geraniol	240

12.	1a,3,3,4,6,6-Hexamethyl-1a,2,3,4,5,6,7,7a-octahydronaphtho[2,3- <i>b</i>]oxirene at 50% in triethyl citrate	50
13.	(3Z)-Hex-3-en-1-ol	4
14.	(3Z)-Hex-3-en-1-yl acetate	4
5 15.	2-Hexylcyclopent-2-en-1-one at 10% in DPG	12
16.	2-Hexyl-3-phenylprop-2-enal	80
17.	3-(4-Isobutylphenyl)-2-methylpropanal	200
18.	Methyl dihydrojasmonate	80
19.	8-Methyl- α -ionone	60
10 20.	γ -Undecalactone	10
21.	2- <i>tert</i> -Butyl-5-methyl-2-propyltetrahydrofuran	40
		1000

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2-*tert*-Butyl-5-methyl-2-propyltetrahydrofuran adds to this floral-fruity raspberry accord a sophisticated blackcurrant note, which conveys diffusivity, freshness and naturalness. Moreover, this compound rounds the composition off and increases the volume, without incorporating unpleasant sulphury connotation as is usually the case when employing blackcurrant odorants. Thereby, it turns this otherwise plain fruity accord into a solid foundation for a multifacet female fragrance.

Example 12: Fruity-Green Fantasy Fragrance for Use in Cosmetics

25

	Ingredient	Parts per weight
1.	1,3-Benzodioxole-5-carboxaldehyde	16
2.	2- <i>tert</i> -Butylcyclohexyl acetate	80
30 3.	Coumarin	24
4.	Dihydromyrcenol	80
5.	Ethyl acetoacetate	32
6.	Ethyl 1,3-dioxolan-2-yl-2-methylacetate	16
7.	Ethyl 3-methyl-3-phenylglycidate	4
35 8.	Ethyl oxyhydrate	4

	9.	(3Z)-Hex-3-en-1-yl acetate at 10% in DPG	8
	10.	Hexyl acetate	16
	11.	4-(4-Hydroxyphenyl)-2-butanone (N112) at 10% in DPG	8
	12.	α -Ionone	16
5	13.	Iso-E-Super	32
	14.	Linalool	160
	15.	Linalyl acetate	130
	16.	Nonyl acetate	50
	17.	3-Phenylprop-2-enal	4
10	18.	4-Methoxybenzaldehyde	80
	19.	8-Methyl- α -ionone	160
	20.	5-Methyl-3-heptanone oxime	16
	21.	1,7,7-Trimethyl-2'-(isopropyl)spiro-(bicyclo[2.2.1]heptane-2,4'-[1,3]dioxane) at 50% in isopropyl myristate	32
15	22.	γ -Undecalactone	32
	23.	2-(3',3'-Dimethylcyclohexyl)-2,5-dimethyl-2,5-dihydrofuran	10
			1010

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Though 2-(3',3'-dimethylcyclohexyl)-2,5-dimethyl-2,5-dihydrofuran is used in 1% only, it harmonizes the composition with a sophisticated, sparkling touch of blackcurrant. It brings naturalness to the composition and rounds off the fruity aspects of this fantasy fragrance for use in cosmetics.

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Example 13: Red Berries Fragrance for Use in Shampoo

	Ingredient	Parts per weight
30	1. Allyl hexanoate	0.40
	2. Allyl pentyloxyacetate	0.50
	3. Benzaldehyde	2.00
	4. 1,3-Benzodioxole-5-carboxaldehyde	6.00
35	5. 2- <i>tert</i> -Butylcyclohexyl acetate	70.00

30110 PCT

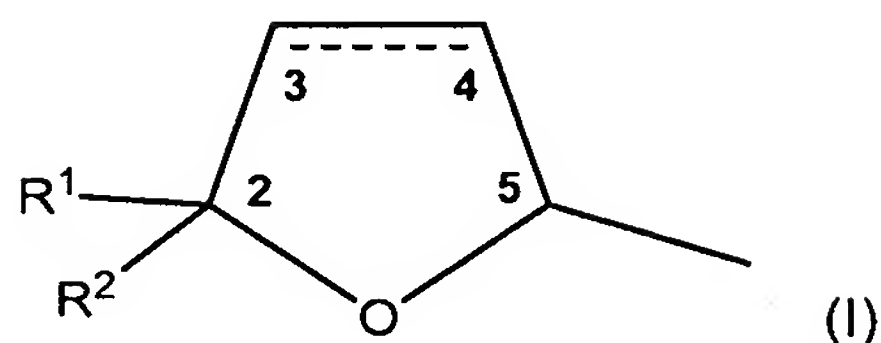
	6.	4- <i>tert</i> -Butylcyclohexyl acetate	1.00
	7.	2-Cyclohexyl-2-phenylacetonitrile	5.00
	8.	α -Damascone	1.00
	9.	Decanal	0.60
5	10.	Dihydromyrcenol	15.00
	11.	Dihydro-5-pentyl-2(3 <i>H</i>)-furanone	10.00
	12.	2,4-Dimethylcyclohex-3-enecarboxaldehyde	4.00
	13.	3,7-Dimethylnona-2,6-dienenitrile	0.20
	14.	3,7-Dimethylnona-1,6-dien-3-ol	60.00
10	15.	1,1-Dimethyl-2-phenylethyl butanoate	3.00
	16.	Dipropylene glycol (DPG)	57.91
	17.	Dodecahydro-3a,6,6,9a-tetramethyl-naphto-(2,1b)-furan	0.10
	18.	Ethyl acetate	1.00
	19.	Ethyl acetoacetate	1.00
15	20.	Ethyl butanoate	0.20
	21.	Ethyl 2-ethyl-6,6-dimethylcyclohex-2-enecarboxylate	5.00
	22.	Ethyl heptanoate	1.00
	23.	Ethyl maltol	0.10
	24.	Ethyl 2-methylbutanoate	2.00
20	25.	6-Ethyl-3-methyloct-6-en-1-ol	5.00
	26.	Ethyl 3-methyl-3-phenylglycidate	7.00
	27.	<i>trans</i> -8-Ethyl-1-oxaspiro[4.5]decan-2-one at 1% in triethyl citrate	2.00
	28.	Ethyl vanillin	0.05
	29.	4,6,6,7,8,8-Hexamethyl-1,3,4,6,7,8-hexahydrocyclopenta[g]benzopyran	
25		at 75% in diethyl phthalate	400.00
	30.	Hexyl salicylate	140.00
	31.	1-(4-Hydroxyphenyl)butan-3-one	70.00
	32.	β -Ionone	28.00
	33.	Isoamyl acetate	5.00
30	34.	Iso-E-Super	50.00
	35.	(-)- <i>p</i> -Menthan-3-ol	0.50
	36.	4,7-Methano-1H-3a,4,5,6,7,7a-hexahydro-inden-6-yl acetate	5.00
	37.	4-Methoxybenzaldehyde	0.50
	38.	Methoxyphenylbutanone	2.00
35	39.	Methyl anthranilate	0.20

	40.	4-Methyldec-3-en-5-ol	0.20
	41.	Methyl dihydrojasmonate	40.00
	42.	2-Methyl-3-(4-isopropylphenyl)propanal	1.30
	43.	(<i>E</i>)-Methyl octa-4,7-dienoate	0.30
5	44.	(10 <i>Z</i>)-13-Methyloxacyclopentadec-10-en-2-one	5.00
	45.	<i>cis</i> -2-Methyl-4-propyl-1,3-oxathiane at 50% in triethyl citrate	0.09
	46.	Phenoxyethyl isobutanoate	243.00
	47.	2-Phenylethanol	30.00
	48.	1-Phenylethyl acetate	2.00
10	49.	Prenyl acetate	0.30
	50.	2,4,4,7-Tetramethylnona-6,8-dien-3-one oxime at 1% in benzyl laurate	0.50
	51.	1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)hepta-1,6-dien-3-one	0.05
	52.	γ -Undecalactone	5.00
	53.	2-(3',3'-Dimethylcyclohexyl)-2,5-dimethyl-2,5-dihydrofuran	10.00
15	<hr/>		1300
	<hr/>		

20 In a dosage of less than 1%, 2-(3',3'-dimethylcyclohexyl)-2,5-dimethyl-2,5-dihydrofuran adds to the composition a fruity, juicy aspect that imparts a sweet, sugary yet natural tonality. The dihydrofuran blends very well with the other compounds of this fruity fragrance, makes it rounder and more complex. Its blackcurrant note harmonizes very well with the musk and the floral ionone accord, without dominating the fragrance.

Claims

1. A compound of formula (I)



wherein

R¹ is methyl, ethyl, propyl or iso-propyl;

R² is a branched C₄ - C₇ alkyl, C₅ - C₈ cycloalkyl, or mono- or disubstituted C₅ or C₆ cycloalkyl; and

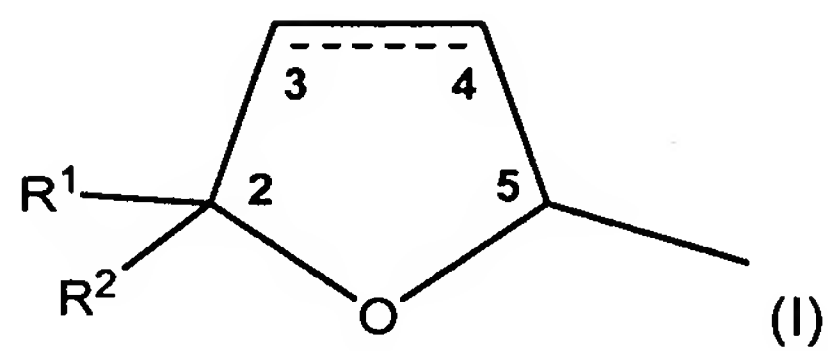
the bond between C-3 and C-4 is a single bond, or the dotted line together with the bond between C-3 and C-4 represents a double bond.

2. A compound according to claim 1 selected from the group consisting of 2-*tert*-butyl-5-methyl-2-propyl-2,5-dihydrofuran, 2-*tert*-butyl-5-methyl-2-propyltetrahydrofuran, 2-*tert*-butyl-2-isopropyl-5-methyl-2,5-dihydrofuran, 2-*tert*-butyl-2-isopropyl-5-methyltetrahydrofuran, 2-*tert*-butyl-2-ethyl-5-methyl-2,5-dihydrofuran, 2-*tert*-butyl-2-ethyl-5-methyltetrahydrofuran, 2-*tert*-butyl-2,5-dimethyl-2,5-dihydrofuran, 2-*tert*-butyl-2,5-dimethyltetrahydrofuran, 2-(3',3'-dimethylcyclohexyl)-2,5-dimethyl-2,5-dihydrofuran, and 2-(3',3'-dimethylcyclohexyl)-2,5-dimethyltetrahydrofuran.
3. Use as odorant of a compound of formula (I) as defined by claim 1 or 2..
4. A flavour or fragrance composition comprising a compound of formula (I) as defined in claim 1 or 2.
5. A method of manufacturing a flavour or fragrance composition, comprising the step of incorporating a compound of formula (I) as defined in claim 1 or 2 into a base material.

6. A method of manufacturing a fragrance application, comprising the incorporation of a compound of formula (I) as defined in claim 1 or 2.
7. A method according to claim 6 wherein the fragrance application is selected from the group consisting of perfumes, household products, laundry products, body care products and cosmetics.

Abstract

2,2-Disubstituted 5-methyl-2,5-dihydro- and 2,2-disubstituted 5-methyl-tetrahydrofurans of formula (I)



wherein R¹ and R² have the same meaning as described in the specification are useful as odorants.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CH2005/000137

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D307/04 C07D307/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 22 April 2001 (2001-04-22), XP002337262 retrieved from STN Database accession no. 1963:408398 abstract & P. GOLDFINGER: "Reactions of halogen atoms" PURE & APPLIED CHEMISTRY, vol. 5, 1962, pages 423-440, GB; PERGAMON PRESS, OXFORD -----	1,2
A	US 4 336 197 A (FANKHAUSER ET AL) 22 June 1982 (1982-06-22) column 1, Formula (I) column 1, lines 60,61 column 2, line 55 - line 58 column 3, line 4 - line 6 -----	1-7



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

21 July 2005

Date of mailing of the international search report

02/08/2005

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CH2005/000137

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			EP 0033959 A1 19-08-1981
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